

REQUEST FOR ACCESS OF ABANDONED APPLICATION UNDER 37 CFR 1.14(a)

In re Application of

Queen et al

Application Number

07/310,252

Filed

2/13/89

Group Art Unit

Examiner

Paper No. ~~33~~ ~~34~~ ~~35~~ ~~36~~ ~~37~~ ~~38~~ ~~39~~ ~~40~~ ~~41~~ ~~42~~ ~~43~~ ~~44~~ ~~45~~ ~~46~~ ~~47~~ ~~48~~ ~~49~~ ~~50~~ ~~51~~ ~~52~~ ~~53~~ ~~54~~ ~~55~~ ~~56~~ ~~57~~ ~~58~~ ~~59~~ ~~60~~ ~~61~~ ~~62~~ ~~63~~ ~~64~~ ~~65~~ ~~66~~ ~~67~~ ~~68~~ ~~69~~ ~~70~~ ~~71~~ ~~72~~ ~~73~~ ~~74~~ ~~75~~ ~~76~~ ~~77~~ ~~78~~ ~~79~~ ~~80~~ ~~81~~ ~~82~~ ~~83~~ ~~84~~ ~~85~~ ~~86~~ ~~87~~ ~~88~~ ~~89~~ ~~90~~ ~~91~~ ~~92~~ ~~93~~ ~~94~~ ~~95~~ ~~96~~ ~~97~~ ~~98~~ ~~99~~ ~~100~~ ~~101~~ ~~102~~ ~~103~~ ~~104~~ ~~105~~ ~~106~~ ~~107~~ ~~108~~ ~~109~~ ~~110~~ ~~111~~ ~~112~~ ~~113~~ ~~114~~ ~~115~~ ~~116~~ ~~117~~ ~~118~~ ~~119~~ ~~120~~ ~~121~~ ~~122~~ ~~123~~ ~~124~~ ~~125~~ ~~126~~ ~~127~~ ~~128~~ ~~129~~ ~~130~~ ~~131~~ ~~132~~ ~~133~~ ~~134~~ ~~135~~ ~~136~~ ~~137~~ ~~138~~ ~~139~~ ~~140~~ ~~141~~ ~~142~~ ~~143~~ ~~144~~ ~~145~~ ~~146~~ ~~147~~ ~~148~~ ~~149~~ ~~150~~ ~~151~~ ~~152~~ ~~153~~ ~~154~~ ~~155~~ ~~156~~ ~~157~~ ~~158~~ ~~159~~ ~~160~~ ~~161~~ ~~162~~ ~~163~~ ~~164~~ ~~165~~ ~~166~~ ~~167~~ ~~168~~ ~~169~~ ~~170~~ ~~171~~ ~~172~~ ~~173~~ ~~174~~ ~~175~~ ~~176~~ ~~177~~ ~~178~~ ~~179~~ ~~180~~ ~~181~~ ~~182~~ ~~183~~ ~~184~~ ~~185~~ ~~186~~ ~~187~~ ~~188~~ ~~189~~ ~~190~~ ~~191~~ ~~192~~ ~~193~~ ~~194~~ ~~195~~ ~~196~~ ~~197~~ ~~198~~ ~~199~~ ~~200~~ ~~201~~ ~~202~~ ~~203~~ ~~204~~ ~~205~~ ~~206~~ ~~207~~ ~~208~~ ~~209~~ ~~210~~ ~~211~~ ~~212~~ ~~213~~ ~~214~~ ~~215~~ ~~216~~ ~~217~~ ~~218~~ ~~219~~ ~~220~~ ~~221~~ ~~222~~ ~~223~~ ~~224~~ ~~225~~ ~~226~~ ~~227~~ ~~228~~ ~~229~~ ~~230~~ ~~231~~ ~~232~~ ~~233~~ ~~234~~ ~~235~~ ~~236~~ ~~237~~ ~~238~~ ~~239~~ ~~240~~ ~~241~~ ~~242~~ ~~243~~ ~~244~~ ~~245~~ ~~246~~ ~~247~~ ~~248~~ ~~249~~ ~~250~~ ~~251~~ ~~252~~ ~~253~~ ~~254~~ ~~255~~ ~~256~~ ~~257~~ ~~258~~ ~~259~~ ~~260~~ ~~261~~ ~~262~~ ~~263~~ ~~264~~ ~~265~~ ~~266~~ ~~267~~ ~~268~~ ~~269~~ ~~270~~ ~~271~~ ~~272~~ ~~273~~ ~~274~~ ~~275~~ ~~276~~ ~~277~~ ~~278~~ ~~279~~ ~~280~~ ~~281~~ ~~282~~ ~~283~~ ~~284~~ ~~285~~ ~~286~~ ~~287~~ ~~288~~ ~~289~~ ~~290~~ ~~291~~ ~~292~~ ~~293~~ ~~294~~ ~~295~~ ~~296~~ ~~297~~ ~~298~~ ~~299~~ ~~300~~ ~~301~~ ~~302~~ ~~303~~ ~~304~~ ~~305~~ ~~306~~ ~~307~~ ~~308~~ ~~309~~ ~~310~~ ~~311~~ ~~312~~ ~~313~~ ~~314~~ ~~315~~ ~~316~~ ~~317~~ ~~318~~ ~~319~~ ~~320~~ ~~321~~ ~~322~~ ~~323~~ ~~324~~ ~~325~~ ~~326~~ ~~327~~ ~~328~~ ~~329~~ ~~330~~ ~~331~~ ~~332~~ ~~333~~ ~~334~~ ~~335~~ ~~336~~ ~~337~~ ~~338~~ ~~339~~ ~~340~~ ~~341~~ ~~342~~ ~~343~~ ~~344~~ ~~345~~ ~~346~~ ~~347~~ ~~348~~ ~~349~~ ~~350~~ ~~351~~ ~~352~~ ~~353~~ ~~354~~ ~~355~~ ~~356~~ ~~357~~ ~~358~~ ~~359~~ ~~360~~ ~~361~~ ~~362~~ ~~363~~ ~~364~~ ~~365~~ ~~366~~ ~~367~~ ~~368~~ ~~369~~ ~~370~~ ~~371~~ ~~372~~ ~~373~~ ~~374~~ ~~375~~ ~~376~~ ~~377~~ ~~378~~ ~~379~~ ~~380~~ ~~381~~ ~~382~~ ~~383~~ ~~384~~ ~~385~~ ~~386~~ ~~387~~ ~~388~~ ~~389~~ ~~390~~ ~~391~~ ~~392~~ ~~393~~ ~~394~~ ~~395~~ ~~396~~ ~~397~~ ~~398~~ ~~399~~ ~~400~~ ~~401~~ ~~402~~ ~~403~~ ~~404~~ ~~405~~ ~~406~~ ~~407~~ ~~408~~ ~~409~~ ~~410~~ ~~411~~ ~~412~~ ~~413~~ ~~414~~ ~~415~~ ~~416~~ ~~417~~ ~~418~~ ~~419~~ ~~420~~ ~~421~~ ~~422~~ ~~423~~ ~~424~~ ~~425~~ ~~426~~ ~~427~~ ~~428~~ ~~429~~ ~~430~~ ~~431~~ ~~432~~ ~~433~~ ~~434~~ ~~435~~ ~~436~~ ~~437~~ ~~438~~ ~~439~~ ~~440~~ ~~441~~ ~~442~~ ~~443~~ ~~444~~ ~~445~~ ~~446~~ ~~447~~ ~~448~~ ~~449~~ ~~450~~ ~~451~~ ~~452~~ ~~453~~ ~~454~~ ~~455~~ ~~456~~ ~~457~~ ~~458~~ ~~459~~ ~~460~~ ~~461~~ ~~462~~ ~~463~~ ~~464~~ ~~465~~ ~~466~~ ~~467~~ ~~468~~ ~~469~~ ~~470~~ ~~471~~ ~~472~~ ~~473~~ ~~474~~ ~~475~~ ~~476~~ ~~477~~ ~~478~~ ~~479~~ ~~480~~ ~~481~~ ~~482~~ ~~483~~ ~~484~~ ~~485~~ ~~486~~ ~~487~~ ~~488~~ ~~489~~ ~~490~~ ~~491~~ ~~492~~ ~~493~~ ~~494~~ ~~495~~ ~~496~~ ~~497~~ ~~498~~ ~~499~~ ~~500~~ ~~501~~ ~~502~~ ~~503~~ ~~504~~ ~~505~~ ~~506~~ ~~507~~ ~~508~~ ~~509~~ ~~510~~ ~~511~~ ~~512~~ ~~513~~ ~~514~~ ~~515~~ ~~516~~ ~~517~~ ~~518~~ ~~519~~ ~~520~~ ~~521~~ ~~522~~ ~~523~~ ~~524~~ ~~525~~ ~~526~~ ~~527~~ ~~528~~ ~~529~~ ~~530~~ ~~531~~ ~~532~~ ~~533~~ ~~534~~ ~~535~~ ~~536~~ ~~537~~ ~~538~~ ~~539~~ ~~540~~ ~~541~~ ~~542~~ ~~543~~ ~~544~~ ~~545~~ ~~546~~ ~~547~~ ~~548~~ ~~549~~ ~~550~~ ~~551~~ ~~552~~ ~~553~~ ~~554~~ ~~555~~ ~~556~~ ~~557~~ ~~558~~ ~~559~~ ~~560~~ ~~561~~ ~~562~~ ~~563~~ ~~564~~ ~~565~~ ~~566~~ ~~567~~ ~~568~~ ~~569~~ ~~570~~ ~~571~~ ~~572~~ ~~573~~ ~~574~~ ~~575~~ ~~576~~ ~~577~~ ~~578~~ ~~579~~ ~~580~~ ~~581~~ ~~582~~ ~~583~~ ~~584~~ ~~585~~ ~~586~~ ~~587~~ ~~588~~ ~~589~~ ~~590~~ ~~591~~ ~~592~~ ~~593~~ ~~594~~ ~~595~~ ~~596~~ ~~597~~ ~~598~~ ~~599~~ ~~600~~ ~~601~~ ~~602~~ ~~603~~ ~~604~~ ~~605~~ ~~606~~ ~~607~~ ~~608~~ ~~609~~ ~~610~~ ~~611~~ ~~612~~ ~~613~~ ~~614~~ ~~615~~ ~~616~~ ~~617~~ ~~618~~ ~~619~~ ~~620~~ ~~621~~ ~~622~~ ~~623~~ ~~624~~ ~~625~~ ~~626~~ ~~627~~ ~~628~~ ~~629~~ ~~630~~ ~~631~~ ~~632~~ ~~633~~ ~~634~~ ~~635~~ ~~636~~ ~~637~~ ~~638~~ ~~639~~ ~~640~~ ~~641~~ ~~642~~ ~~643~~ ~~644~~ ~~645~~ ~~646~~ ~~647~~ ~~648~~ ~~649~~ ~~650~~ ~~651~~ ~~652~~ ~~653~~ ~~654~~ ~~655~~ ~~656~~ ~~657~~ ~~658~~ ~~659~~ ~~660~~ ~~661~~ ~~662~~ ~~663~~ ~~664~~ ~~665~~ ~~666~~ ~~667~~ ~~668~~ ~~669~~ ~~670~~ ~~671~~ ~~672~~ ~~673~~ ~~674~~ ~~675~~ ~~676~~ ~~677~~ ~~678~~ ~~679~~ ~~680~~ ~~681~~ ~~682~~ ~~683~~ ~~684~~ ~~685~~ ~~686~~ ~~687~~ ~~688~~ ~~689~~ ~~690~~ ~~691~~ ~~692~~ ~~693~~ ~~694~~ ~~695~~ ~~696~~ ~~697~~ ~~698~~ ~~699~~ ~~700~~ ~~701~~ ~~702~~ ~~703~~ ~~704~~ ~~705~~ ~~706~~ ~~707~~ ~~708~~ ~~709~~ ~~710~~ ~~711~~ ~~712~~ ~~713~~ ~~714~~ ~~715~~ ~~716~~ ~~717~~ ~~718~~ ~~719~~ ~~720~~ ~~721~~ ~~722~~ ~~723~~ ~~724~~ ~~725~~ ~~726~~ ~~727~~ ~~728~~ ~~729~~ ~~730~~ ~~731~~ ~~732~~ ~~733~~ ~~734~~ ~~735~~ ~~736~~ ~~737~~ ~~738~~ ~~739~~ ~~740~~ ~~741~~ ~~742~~ ~~743~~ ~~744~~ ~~745~~ ~~746~~ ~~747~~ ~~748~~ ~~749~~ ~~750~~ ~~751~~ ~~752~~ ~~753~~ ~~754~~ ~~755~~ ~~756~~ ~~757~~ ~~758~~ ~~759~~ ~~760~~ ~~761~~ ~~762~~ ~~763~~ ~~764~~ ~~765~~ ~~766~~ ~~767~~ ~~768~~ ~~769~~ ~~770~~ ~~771~~ ~~772~~ ~~773~~ ~~774~~ ~~775~~ ~~776~~ ~~777~~ ~~778~~ ~~779~~ ~~780~~ ~~781~~ ~~782~~ ~~783~~ ~~784~~ ~~785~~ ~~786~~ ~~787~~ ~~788~~ ~~789~~ ~~790~~ ~~791~~ ~~792~~ ~~793~~ ~~794~~ ~~795~~ ~~796~~ ~~797~~ ~~798~~ ~~799~~ ~~800~~ ~~801~~ ~~802~~ ~~803~~ ~~804~~ ~~805~~ ~~806~~ ~~807~~ ~~808~~ ~~809~~ ~~810~~ ~~811~~ ~~812~~ ~~813~~ ~~814~~ ~~815~~ ~~816~~ ~~817~~ ~~818~~ ~~819~~ ~~820~~ ~~821~~ ~~822~~ ~~823~~ ~~824~~ ~~825~~ ~~826~~ ~~827~~ ~~828~~ ~~829~~ ~~830~~ ~~831~~ ~~832~~ ~~833~~ ~~834~~ ~~835~~ ~~836~~ ~~837~~ ~~838~~ ~~839~~ ~~840~~ ~~841~~ ~~842~~ ~~843~~ ~~844~~ ~~845~~ ~~846~~ ~~847~~ ~~848~~ ~~849~~ ~~850~~ ~~851~~ ~~852~~ ~~853~~ ~~854~~ ~~855~~ ~~856~~ ~~857~~ ~~858~~ ~~859~~ ~~860~~ ~~861~~ ~~862~~ ~~863~~ ~~864~~ ~~865~~ ~~866~~ ~~867~~ ~~868~~ ~~869~~ ~~870~~ ~~871~~ ~~872~~ ~~873~~ ~~874~~ ~~875~~ ~~876~~ ~~877~~ ~~878~~ ~~879~~ ~~880~~ ~~881~~ ~~882~~ ~~883~~ ~~884~~ ~~885~~ ~~886~~ ~~887~~ ~~888~~ ~~889~~ ~~890~~ ~~891~~ ~~892~~ ~~893~~ ~~894~~ ~~895~~ ~~896~~ ~~897~~ ~~898~~ ~~899~~ ~~900~~ ~~901~~ ~~902~~ ~~903~~ ~~904~~ ~~905~~ ~~906~~ ~~907~~ ~~908~~ ~~909~~ ~~910~~ ~~911~~ ~~912~~ ~~913~~ ~~914~~ ~~915~~ ~~916~~ ~~917~~ ~~918~~ ~~919~~ ~~920~~ ~~921~~ ~~922~~ ~~923~~ ~~924~~ ~~925~~ ~~926~~ ~~927~~ ~~928~~ ~~929~~ ~~930~~ ~~931~~ ~~932~~ ~~933~~ ~~934~~ ~~935~~ ~~936~~ ~~937~~ ~~938~~ ~~939~~ ~~940~~ ~~941~~ ~~942~~ ~~943~~ ~~944~~ ~~945~~ ~~946~~ ~~947~~ ~~948~~ ~~949~~ ~~950~~ ~~951~~ ~~952~~ ~~953~~ ~~954~~ ~~955~~ ~~956~~ ~~957~~ ~~958~~ ~~959~~ ~~960~~ ~~961~~ ~~962~~ ~~963~~ ~~964~~ ~~965~~ ~~966~~ ~~967~~ ~~968~~ ~~969~~ ~~970~~ ~~971~~ ~~972~~ ~~973~~ ~~974~~ ~~975~~ ~~976~~ ~~977~~ ~~978~~ ~~979~~ ~~980~~ ~~981~~ ~~982~~ ~~983~~ ~~984~~ ~~985~~ ~~986~~ ~~987~~ ~~988~~ ~~989~~ ~~990~~ ~~991~~ ~~992~~ ~~993~~ ~~994~~ ~~995~~ ~~996~~ ~~997~~ ~~998~~ ~~999~~ ~~1000~~ ~~1001~~ ~~1002~~ ~~1003~~ ~~1004~~ ~~1005~~ ~~1006~~ ~~1007~~ ~~1008~~ ~~1009~~ ~~1010~~ ~~1011~~ ~~1012~~ ~~1013~~ ~~1014~~ ~~1015~~ ~~1016~~ ~~1017~~ ~~1018~~ ~~1019~~ ~~1020~~ ~~1021~~ ~~1022~~ ~~1023~~ ~~1024~~ ~~1025~~ ~~1026~~ ~~1027~~ ~~1028~~ ~~1029~~ ~~1030~~ ~~1031~~ ~~1032~~ ~~1033~~ ~~1034~~ ~~1035~~ ~~1036~~ ~~1037~~ ~~1038~~ ~~1039~~ ~~1040~~ ~~1041~~ ~~1042~~ ~~1043~~ ~~1044~~ ~~1045~~ ~~1046~~ ~~1047~~ ~~1048~~ ~~1049~~ ~~1050~~ ~~1051~~ ~~1052~~ ~~1053~~ ~~1054~~ ~~1055~~ ~~1056~~ ~~1057~~ ~~1058~~ ~~1059~~ ~~1060~~ ~~1061~~ ~~1062~~ ~~1063~~ ~~1064~~ ~~1065~~ ~~1066~~ ~~1067~~ ~~1068~~ ~~1069~~ ~~1070~~ ~~1071~~ ~~1072~~ ~~1073~~ ~~1074~~ ~~1075~~ ~~1076~~ ~~1077~~ ~~1078~~ ~~1079~~ ~~1080~~ ~~1081~~ ~~1082~~ ~~1083~~ ~~1084~~ ~~1085~~ ~~1086~~ ~~1087~~ ~~1088~~ ~~1089~~ ~~1090~~ ~~1091~~ ~~1092~~ ~~1093~~ ~~1094~~ ~~1095~~ ~~1096~~ ~~1097~~ ~~1098~~ ~~1099~~ ~~1100~~ ~~1101~~ ~~1102~~ ~~1103~~ ~~1104~~ ~~1105~~ ~~1106~~ ~~1107~~ ~~1108~~ ~~1109~~ ~~1110~~ ~~1111~~ ~~1112~~ ~~1113~~ ~~1114~~ ~~1115~~ ~~1116~~ ~~1117~~ ~~1118~~ ~~1119~~ ~~1120~~ ~~1121~~ ~~1122~~ ~~1123~~ ~~1124~~ ~~1125~~ ~~1126~~ ~~1127~~ ~~1128~~ ~~1129~~ ~~1130~~ ~~1131~~ ~~1132~~ ~~1133~~ ~~1134~~ ~~1135~~ ~~1136~~ ~~1137~~ ~~1138~~ ~~1139~~ ~~1140~~ ~~1141~~ ~~1142~~ ~~1143~~ ~~1144~~ ~~1145~~ ~~1146~~ ~~1147~~ ~~1148~~ ~~1149~~ ~~1150~~ ~~1151~~ ~~1152~~ ~~1153~~ ~~1154~~ ~~1155~~ ~~1156~~ ~~1157~~ ~~1158~~ ~~1159~~ ~~1160~~ ~~1161~~ ~~1162~~ ~~1163~~ ~~1164~~ ~~1165~~ ~~1166~~ ~~1167~~ ~~1168~~ ~~1169~~ ~~1170~~ ~~1171~~ ~~1172~~ ~~1173~~ ~~1174~~ ~~1175~~ ~~1176~~ ~~1177~~ ~~1178~~ ~~1179~~ ~~1180~~ ~~1181~~ ~~1182~~ ~~1183~~ ~~1184~~ ~~1185~~ ~~1186~~ ~~1187~~ ~~1188~~ ~~1189~~ ~~1190~~ ~~1191~~ ~~1192~~ ~~1193~~ ~~1194~~ ~~1195~~ ~~1196~~ ~~1197~~ ~~1198~~ ~~1199~~ ~~1200~~ ~~1201~~ ~~1202~~ ~~1203~~ ~~1204~~ ~~1205~~ ~~1206~~ ~~1207~~ ~~1208~~ ~~1209~~ ~~1210~~ ~~1211~~ ~~1212~~ ~~1213~~ ~~1214~~ ~~1215~~ ~~1216~~ ~~1217~~ ~~1218~~ ~~1219~~ ~~1220~~ ~~1221~~ ~~1222~~ ~~1223~~ ~~1224~~ ~~1225~~ ~~1226~~ ~~1227~~ ~~1228~~ ~~1229~~ ~~1230~~ ~~1231~~ ~~1232~~ ~~1233~~ ~~1234~~ ~~1235~~ ~~1236~~ ~~1237~~ ~~1238~~ ~~1239~~ ~~1240~~ ~~1241~~ ~~1242~~ ~~1243~~ ~~1244~~ ~~1245~~ ~~1246~~ ~~1247~~ ~~1248~~ ~~1249~~ ~~1250~~ ~~1251~~ ~~1252~~ ~~1253~~ ~~1254~~ ~~1255~~ ~~1256~~ ~~1257~~ ~~1258~~ ~~1259~~ ~~1260~~ ~~1261~~ ~~1262~~ ~~1263~~ ~~1264~~ ~~1265~~ ~~1266~~ ~~1267~~ ~~1268~~ ~~1269~~ ~~1270~~ ~~1271~~ ~~1272~~ ~~1273~~ ~~1274~~ ~~1275~~ ~~1276~~ ~~1277~~ ~~1278~~ ~~1279~~ ~~1280~~ ~~1281~~ ~~1282~~ ~~1283~~ ~~1284~~ ~~1285~~ ~~1286~~ ~~1287~~ ~~1288~~ ~~1289~~ ~~1290~~ ~~1291~~ ~~1292~~ ~~1293~~ ~~1294~~ ~~1295~~ ~~1296~~ ~~1297~~ ~~1298~~ ~~1299~~ ~~1300~~ ~~1301~~ ~~1302~~ ~~1303~~ ~~1304~~ ~~1305~~ ~~1306~~ ~~1307~~ ~~1308~~ ~~1309~~ ~~1310~~ ~~1311~~ ~~1312~~ ~~1313~~ ~~1314~~ ~~1315~~ ~~1316~~ ~~1317~~ ~~1318~~ ~~1319~~ ~~1320~~ ~~1321~~ ~~1322~~



US005530101A

United States Patent [19][11] **Patent Number:** **5,530,101****Queen et al.**[45] **Date of Patent:** **Jun. 25, 1996**[54] **HUMANIZED IMMUNOGLOBULINS**[75] **Inventors:** Cary L. Queen, Los Altos; Harold E. Selick, Belmont, both of Calif.[73] **Assignee:** Protein Design Labs, Inc., Mountain View, Calif.[21] **Appl. No.:** 634,278[22] **Filed:** Dec. 19, 1990**Related U.S. Application Data**

[63] Continuation-in-part of Ser. No. 590,274, Sep. 28, 1990, abandoned, and a continuation-in-part of Ser. No. 310,252, Feb. 13, 1989, abandoned, which is a continuation-in-part of Ser. No. 290,975, Dec. 28, 1988, abandoned.

[51] **Int. Cl.⁶** **A61K 39/395; C07K 16/28**[52] **U.S. Cl.** **530/387.3; 530/387.1; 530/388.22; 424/133.1; 424/143.1**[58] **Field of Search** **424/85.8, 133.1, 424/143.1; 530/387, 388.22, 387.1, 387.3**[56] **References Cited****U.S. PATENT DOCUMENTS**

4,816,397	3/1989	Boss et al.	435/68
4,816,567	3/1989	Cabilly et al.	530/387
4,867,973	9/1989	Geers et al.	
5,225,539	7/1993	Winter	

FOREIGN PATENT DOCUMENTS

0171496	2/1986	European Pat. Off.
0173494	3/1986	European Pat. Off.
0184187	6/1986	European Pat. Off.
0239400	9/1987	European Pat. Off.
0266663	6/1988	European Pat. Off.
2188941	10/1987	United Kingdom
WO86/05513	9/1986	WIPO
WO87/02671	5/1987	WIPO
WO89/01783	3/1989	WIPO

OTHER PUBLICATIONSVitteta et al., "Redesigning Nature's Poisons to Create Anti-Tumor Reagents," *Science* 238:1098-1104 (1987).Ellison et al., "The nucleotide sequence of a human immunoglobulin C(gamma)₁ gene", *Nucleic Acids Res.* 10:4071-(1982).Hieter et al., "Cloned Human and Mouse Kappa Immunoglobulin Constant and J Region Genes Conserve homology in Functional Segments", *Cell* 22:197-207 (1980).Sharon et al., "Expression of a V_HC_K chimaeric protein in mouse myeloma cells", *Nature* 309:364-367 (1984).Takeda et al., "Construction of chimaeric processed immunoglobulin genes containing mouse variable and human constant region sequences", *Nature* 314:452-454 (1985).Tan et al., "A Human-Mouse Chimeric Immunoglobulin Gene with a Human Variable Region is Expressed in Mouse Myeloma Cells", *J. Immunol.* 135:3564-3567 (1985).Morrison et al., "Chimeric human antibody molecules: Mouse antigen-binding domains with human constant region domains," *Proc. Natl. Acad. Sci.* 81:6851-6859 (1984).Boulianne et al., "Production of functional chimeric mouse/human antibody," *Nature* 312:643-646 (1984).Neuberger et al., "A hapten-specific chimeric IgE antibody with human physiological effector function," *Nature* 314:268-270 (1985).Morrison, S. L., "Transfectomas Provide Novel Chimeric Antibodies," *Science* 229:1202-1207 (1985).Sahagan et al., "A Genetically Engineered Murine/Human Chimeric Antibody Retains Specificity for Human Tumor-Associated Antigen", *J. Immunol.* 137:1066-1074 (1986).Liu et al., "Expression of mouse:human immunoglobulin heavy-chain cDNA in lymphoid cells", *Gene* 54:33-40 (1987).Better et al., "Escherichia coli Secretion of an Active Chimeric Antibody Fragment", *Science* 240:1041-1043 (1988).Waldmann, T. A., "The Structure, Function, and Expression of Interleukin-2 Receptors on Normal and Malignant Lymphocytes," *Science* 232:727-732 (1986).Leonard et al., "The human receptor for T-cell growth factor," *J. Biol. Chem.* 260:1872-1880 (1985).Farrar, J., "The biochemistry, biology, and role of interleukin-2 in the induction of cytotoxic T cell and antibody-forming B cell receptors," *Immunol. Rev.* 63:129-166 (1982).Greene et al., "Growth of Human T Lymphocytes: An Analysis of Interleukin 2 and Its Cellular receptor", in *Progress in Hematology XIV*, E. Brown ed., Grune and Statton, New York (1986) pp. 283-301.Verhoyen et al., "Reshaping Human Antibodies: Grafting an Antilysozyme Activity", *Science* 239:1534-1536 (1988).Jones et al., "Replacing the complementarity-determining regions in a human antibody with those from a mouse", *Nature* 321:522-525 (1986).Hale et al., "Remission Induction in Non-Hodgkin Lymphoma with Reshaped Human Monoclonal Antibody CAMPATH-1H", *Lancet* Dec. 17, 1988, pp. 1394-1399.Chothia, C. and A. M. Lesk, "Canonical Structures for the Hypervariable Regions of Immunoglobulins", *J. Mol. Biol.* 196:901-917 (1987).

(List continued on next page.)

Primary Examiner—Lila Feisee**Attorney, Agent, or Firm**—Townsend and Townsend and Crew

[57]

ABSTRACT

Novel methods for producing, and compositions of, humanized immunoglobulins having one or more complementarity determining regions (CDR's) and possible additional amino acids from a donor immunoglobulin and a framework region from an accepting human immunoglobulin are provided. Each humanized immunoglobulin chain will usually comprise, in addition to the CDR's, amino acids from the donor immunoglobulin framework that are, e.g., capable of interacting with the CDR's to effect binding affinity, such as one or more amino acids which are immediately adjacent to a CDR in the donor immunoglobulin or those within about 3 Å as predicted by molecular modeling. The heavy and light chains may each be designed by using any one or all of various position criteria. When combined into an intact antibody, the humanized immunoglobulins of the present invention will be substantially non-immunogenic in humans and retain substantially the same affinity as the donor immunoglobulin to the antigen, such as a protein or other compound containing an epitope.

13 Claims, 55 Drawing Sheets